International Journal of Pharmacy and Biological Sciences-IJPBS™ (2019) 9 (2): 924-932
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Review Article | Pharmaceutical Sciences | Open Access | MCI Approved
UGC Approved Journal

A Review on Stem Cells Therapy- A New Treatment for Cerebral Palsy

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Received: 14 Jan 2019 / Accepted: 19 Mar 2019 / Published online: 1 Apr 2019
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Abstract

Cerebral palsy is a neurological disorder caused by non-progressive brain injury (or)malformation that occurs during perinatal stage. CP is caused by many factors like premature birth infection in uterus, lack of Nutrional support during development, lack of oxygen at the time of birth and genetic abnormalities. It affects muscle movement and coordination. Main symptoms-visual and cognitive impairment. Stem cells are the precursors for any cells. These are unspecialized cells which becomes specialized cells such as brain cells, heart cells and muscle cells. Stem cell transplantation is a regenerative therapy that has the potential to replace the damaged cells and non-functional cells in the brain of CP patients. From the clinical trials phase II data, it suggests that it's beneficial in the patient with acute CP when compared to chronic CP patients. Far more research is needed to determine the appropriateness of this therapy.

Keywords

cerebral palsy, stem cells, stem cell transplantation, regenerative therapy, perinatal, neurons/brain cells.

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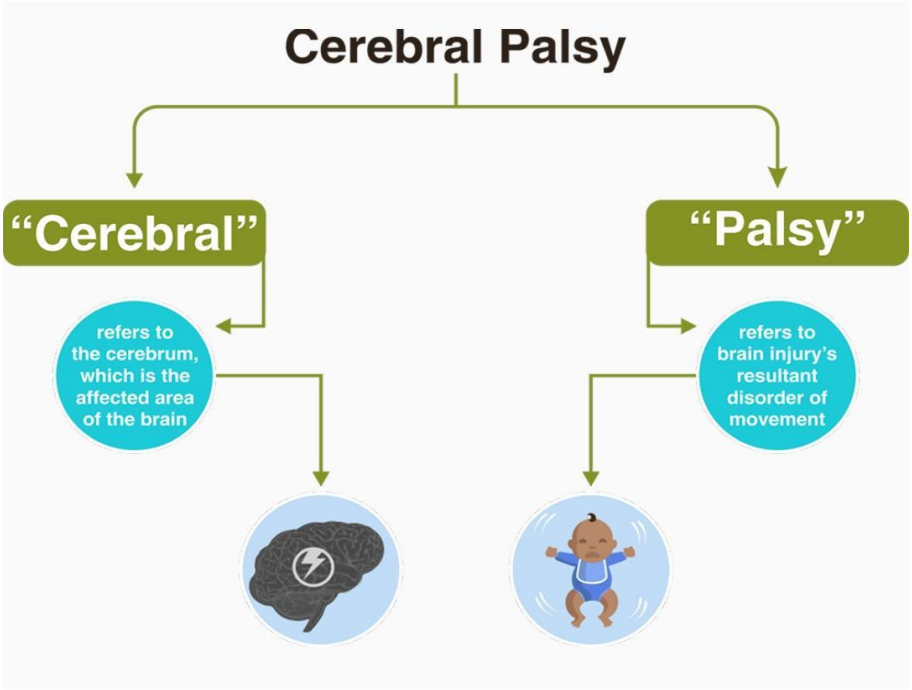
INTRODUCTION

CP is a heterogeneous group of condition. Its defined as non- progressive mortar disability due to an abnormality of the cerebral hemispheres. CP is a complex term used to describe abnormality in brain due to perinatal brain injury [1]. CP is caused by many factors like premature births, infections in uterus, lack of Nutrional support during development, lack of oxygen at the time of birth and genetic abnormality. It causes various neuro-mortar deficits associated with other symptoms like visual and cognitive impairment [2][3][4][8].



Among all the causes, most common cause is lack of blood and oxygen to the brain during fetal development (or) delivery. This is called as hypoxic-ischemic insult. The highly affected cells are Oligodendrocytes. Oligodendrocytes contains white fat layer called myelin sheath. If there is any damage to Oligodendrocytes, this eventually leads to the death of neurons. The lost Oligodendrocytes can be replaced with stem cells [5][9].

Epidemiology: -

The incidence rate is similar both in developed and developing world. It's mainly common in poorer people when compared to rich due to lack of nutrition. Its incidence is 1.3 times greater in males when compared to females. CP occurs in about2.1 per 1000 live births. [24- 26]

Types of cerebral palsy: -

Cerebral palsy is classified based on the motar impairment of the limbs (or) organs and by restrictions to normal physiological activity of an affected person. Classification of CP is mainly based on the gross motor function classification system. The 3 main CP are

1. Spastic CP
2. Ataxic CP
3. Athetoid/dyskinetic CP
4. Nonspecific type is mixed type CP.

Cerebral palsy is also classified based on the topographic distribution of muscle spasticity. In this method the affected children are classified as

1. Diplegic (Bilateral involvement of legs is greater than arms)
2. Hemiplegic (Unilateral involvement)
3. Quadriplegic (Bilateral involvement of arms equal (or)greater than leg)

Spastic Cerebral Palsy: -

This is the most common type which includes 70-80% of the cases. The specific characteristic feature of spastic CP is spasticity (muscle tightness) people with spastic CP may also experience hypertonic and neuromuscular mobility impairment (rather than hypotonia (or) paralyze). This mainly occurs when an upper motor neurons Simon the brain and corticospinal tract(or) the motor cortex damage is present. Due to this damage the neurons (or)nerve receptors in the spine response to gamma- Amino butyric acid is impaired. This leads to effects on speech and bladder control.

Compared to other types, spastic CP is more easily multitude of orthopedic and neurological fronts throughout their lifespan. The early symptoms are arthritis and tendinitis. The best ways modified are physical activity and exercise If not modified with non-pharmacologic Al treatments antispasmodic medication like baclofen. Botulinum toxic (or) neurosurgery named selective dorsal rhizotomy (Eliminates the spasticity by reducing the excitory neural response in nerves causing it) can be performed.

Ataxic Cerebral Palsy: -

This is the 2nd most common type accounting approximately 5-10% of total cerebral palsy. This is caused due to the damage to cerebellar structures. The damage to cerebellum leads to alterations in

muscle movement and balance. They lack coordination of their arms, legs and trunk this decreases the muscle tone and most common manifestation is action tremors, which is especially apparent when carrying out precise movements, like tying laces (or) writing with pen / pencil. The symptoms progress to persistent movements like making handshake. Due to this there will be difficulty in completing their work.

Athetoid Cerebral Palsy: -

It is also called as dyskinetic cerebral palsy. Sometimes it's abbreviated as ADCP. The major affected region is basal ganglia and it forms lesion's during the development of brain due to bilirubin encephalopathy and hypoxic-ischemic brain injury. The major characteristics of ADCP are both hypertonia and hypotonia. This is due to the loss of individuals ability to control muscle tone. It can be diagnosed within 18 months of birth and is primarily based on motor functions and neuroimaging techniques.

It is a non spastic extrapyramidal form of cerebral palsy. ADCP can be divided into two different groups choreoathetoid and dystonic. Choreoathetotic CP is characterized by involuntary movements most predominantly in face and extremities. Dystonic ADCP is characterized by slow, strong contractions, which may occur locally (or) the whole body.

Mixed Cerebral Palsy: -

It has symptoms of athetoid, a toxic, and spastic CP. These three appears simultaneously but varies in their degrees. This may be symptomatic (or) asymptomatic. Treatment of mixed CP is very difficult because it develops unpredictable symptoms over the lifespan. [27-29]

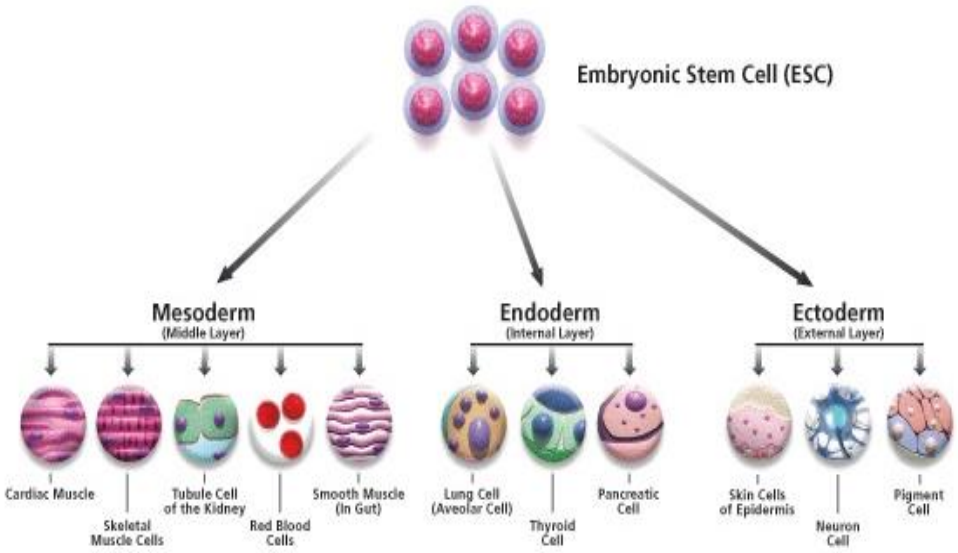
Diagnosis: -

It involves both physical examination as well as histological examination. A general movements assessment involves measuring movements. This occur spontaneously in children less than four months of age. Children who are more severely affected are diagnosed earlier. Abnormal muscle tone, delayed motor development and persistence of primitive reflexes are the main early symptoms of CP. Symptoms and diagnosis typically occur by the age and it is a developmental disability.[30]

Treatment: -

Childhood therapy is aimed at improving gait and walking. Approximately 60% of people with CP are able to walk independently or with aids at adulthood. Treatment may include one or more of the following: physical therapy; occupational therapy; speech therapy; water therapy; drugs to control seizures, alleviate pain, or relax muscle spasms (e.g. benzodiazepines); surgery to correct anatomical abnormalities or release tight muscles; braces and other orthotic devices; rolling walkers; and communication aids such as computers with attached voice synthesizers.[31]

Stem cells are unspecialized cells. After differentiation they become specialized cells. For example, brain cells, heart cells (or) muscle cells [6][7] later these stem cells undergo proliferation into specialized cells called as brain cells [9]. Stem cell transplantation is a regenerative therapy that has the potential of replacing the damaged and non-functional cells. They also provide support to the oligodendrocytes and maiming neurons [3][9].



Potential Sources of Cells: -

1. Mesenchymal stem cells
2. Umbilical cord blood
3. CD34 cells
4. Fetal stem cells
5. Embryonic stem cells
6. Oligodendrocytes progenitor cells
7. progenitor cells
8. Induced pluripotent stem cells

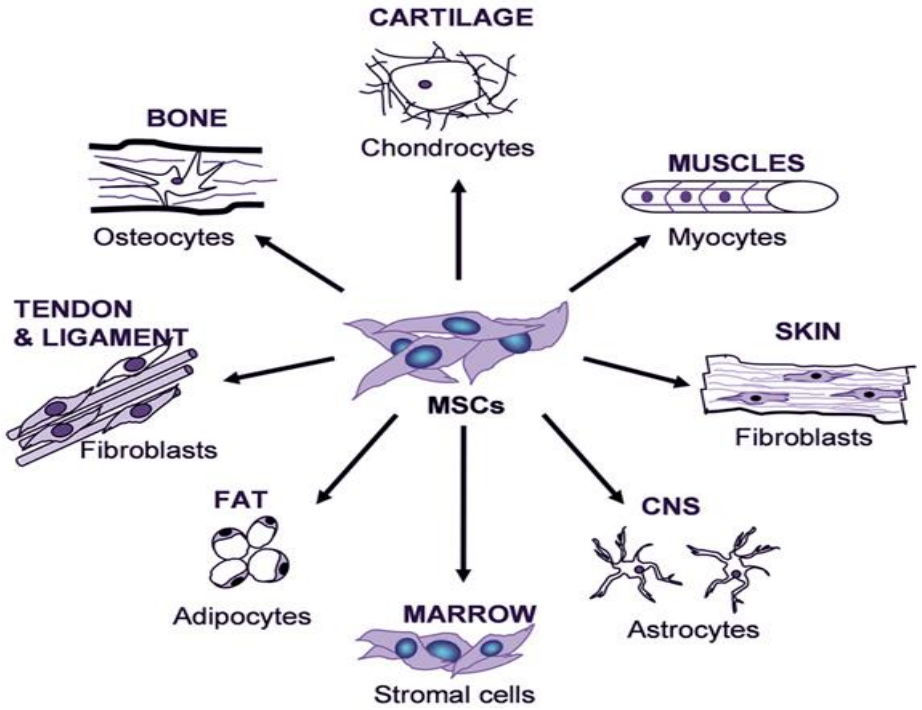
These are the potential cell sources which are being used in experimental animal models. This involves direct implantation of cells into brain parenchyma (or) by a intravenous injection [8][10].

Mesenchymal stem cells (MSCS): -

MSCS are bone macro stromal cells. It is composed of mixture of cell types. Only about 0.001 - 0.01% of the cells in the bone marrow are mesenchymal stem cells**.** They are capable of supporting hematopoiesis by differentiating into multiple cell types. Bone marrow is considered as the primary source of MSCS, secondary are human umbilical cord blood and the tertiary one is some other tissues like adipose tissue, amniotic blood, menstrual blood, perimetrium [4]. Mesenchymal stem cells are characterized by a small cell body with few no. of cell that are long and thin. The cell body contains a large, round nucleus with a prominent nucleolus, which is surrounded by finely dispersed chromatin particles, giving the nucleus a clear appearance.[32]

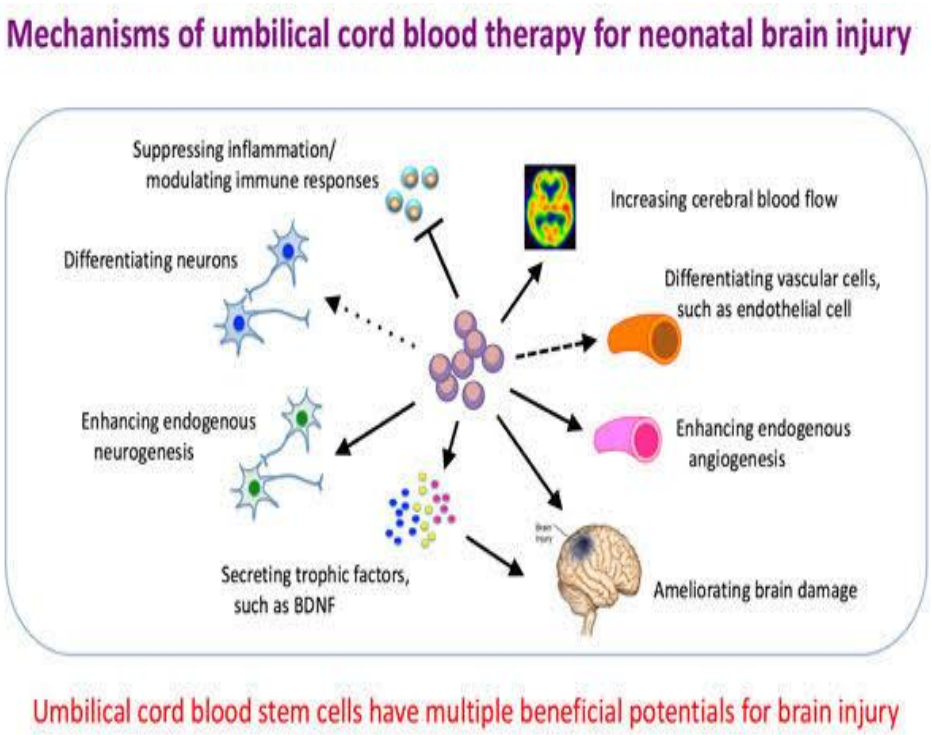
Umbilical cord blood (UCB): -

Umbilical cord blood was once discarded as waste material but is now these are known to be a useful sources of blood stem cells. In recent days UCB is used as popular source of adult stem cells. It causes fewer immune rejections or complications such as Graft versus Host Disease when compared to bone marrow. This means that cord blood does not need to be as perfectly matched to the patient as that in bone marrow. There are number of public and private banks in US and other parents of world. The collection of umbilical cord blood is somewhat controversial because of the question on the utility and preservation in private banks. The minimum dose is 1×10^7 cells/kg. This dose is for cell engraftment therapy. The total cells include not only total nucleated cell fractions but also stem cells.[8][9]



Embryonic Stem Cells: -

Embryonic stem cells (ESCs) are pluripotent stem cells, derived in vitro from 4-7days blastocyte of an embryo, isolated originally from the inner cell mass (ICM). ESCs possess distinctive self-renewal capacity, pluripotency and genomic stability. They are capable of producing all types of lineages in the body. They are promising cells for stem cell therapy. From the very first derivation of ESC's the scientists are keenly focusing of these cells in drug discovery, regenerative therapy and immunotherapy. Due to some ethical issues their use is restricted. [34,35]



CD34cells: -

CD34 was first described on hematopoietic stem cells independently by Civin et al. CD34 cells are usually collected by leukopheresis. CD34 cells are found in bone marrow and umbilical cord blood. They represent the subset of MSCS and are smaller size. They are isolated based on the presence of trans membrane brain glycoprotein as their surface characteristics. CD34 cells may be obtained from phlebotomy. Nonmobilized leukopheresis may yield up to 10^9 mononuclear cells, affording approximately 5 million CD4L34 cells. [8,36,37]

Fetal stem cells: -

They are collected from fetal tissue. The utility of these cells is not well depicted in animal models Aftab et al demonstrated that retinal progenitor cells from donor tissue of 16-18 weeks of gastrointestinal period were able to integrate into host cells. The main use is expression of rhodopsin [8].

Multipotent adult progenitor cells: -

MAPH are derived from bone marrow as well as other tissue sources. Phenotype consists of CD13+FlK1dim-, Ckit-, CD44-, CD45-, MHC classI-, and MHC classII-. Upon differentiation they become into mesenchymal cells. Visceral mesoderm, neuroectoderm and endoderm are potential [11][12].

Oligodendrocytes progenitor cells (OPC): -

OPC is also known as oligodendrocyte precursor cells, NG2-glia or polydendrocytes, are a subtype of glial cells in the central nervous system.[38] OPC are delivered from fetal brain tissue, embryonic stem cells(or) iPSC cells. They are precursors for oligodendrocytes and are also able to differentiate into neurons and astrocytes. After transplanting they are capable of remyelination. [39]

Induced pluripotent stem cells: -

Induced pluripotent stem cells (iPSCs) are generated from adult cells. This occurs by overexpression of four transcription factors. They are Oct 4/3 (octamer-binding transcription factor 4/3), Sox2 (sex determining region Y), Klf4 (kruppel-like factor 4) and c-Myc (Avian Myelocytomatosis virus oncogene cellular homologue). The iPSCs at cellular level are almost similar to ESCs. They are also having the capacity of self-renewal, differentiation potential and the ability to produce germ line competent chimeras. Takahashi et al and Nakagawa et al have generated the iPSCs from adult human fibroblasts.[33]

Mechanism of action in cerebral palsy: -

1. Neuronal cell replacement
2. Astrocyte replacement
3. Microglial cell replacement
4. Blood vessel regeneration
5. Protection of intrinsic cells
6. Blockade of splenic release of inflammatory cells

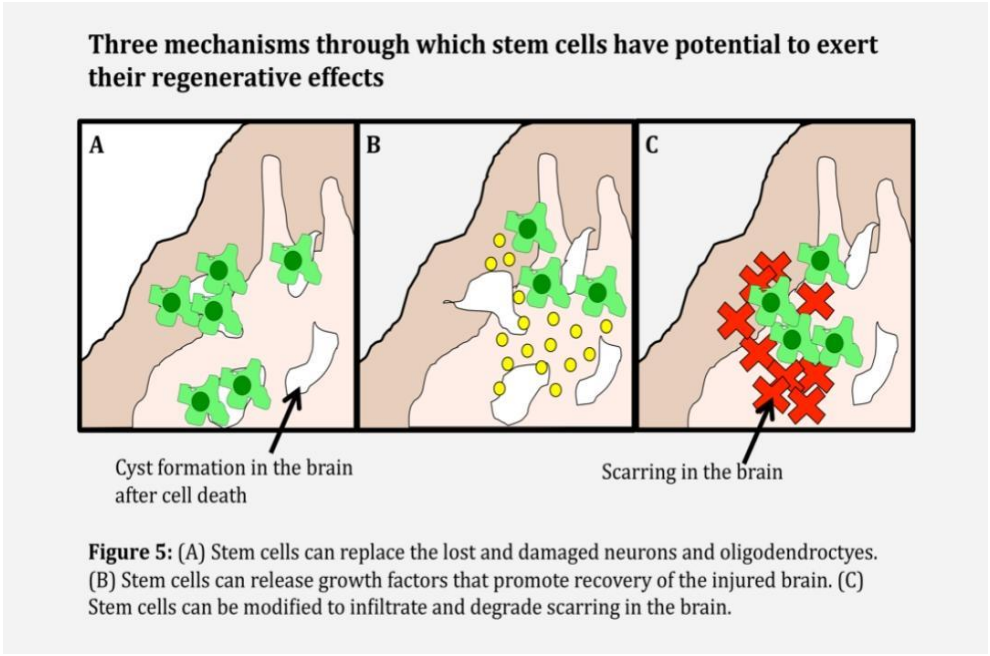
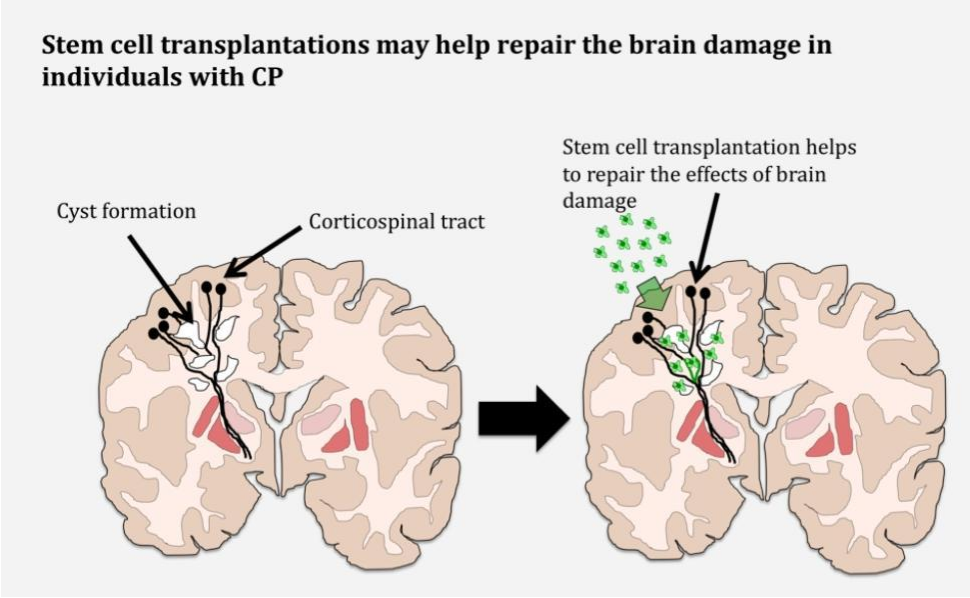


Figure 5: (A) Stem cells can replace the lost and damaged neurons and oligodendroctyes. (B) Stem cells can release growth factors that promote recovery of the injured brain. (C) Stem cells can be modified to infiltrate and degrade scarring in the brain.

The stem cells will replace the damaged cells of nervous system. Only few numbers of adult cells displaying functionality of nervous system. Replacement alone is not highly beneficial in the experimental situation. When compared to adult stem cells, embryonic stem cells(or) iPSC have greater potential for replacement and transformation [13][14][15]. The number of cells involved is quite limited and some may not develop into the normal cells which are similar to cells in neuronal circuitry. The transplanted cells may also develop into astrocytes (or)microglia and functional recovery is unclear [16].



Borlangal et al demonstrated that crude bone marrow forms endothelial cells [17]. Mohamood et al [18] used mesenchymal stem cell injection to demonstrate that transplanted cells are likely to increase the expression of nerve growth factor and brain-derived neurotrophic factor after traumatic injury. Venderama et al showed that umbilical cord blood (UCB) lessened the splenic release of inflammatory cells which protects the brain [19]. In addition to this concept walker et al demonstrated that to injury. This improved the outcomes [20].

Pre-Clinical Trials: -

The researchers are utilized various sources of stem cells like Embryonic stem cells (ESC), mesenchymal stem cells (MSC), induced pluripotent stem cells (iPSC's),neural precursor cells(NPCS)for extracting the stem cells. The study revealed that stem cell transplantation has improved the function of brain and also suggests the positive outcomes in the anatomical changes in brain.

Kids brain Health Brain Network Preclinical research team, Dr.Michael Fehlings and Kermbil Research institute, university health network and university of Toronto are currently working on NPCS and iPSC's for treatment of cerebral palsy.

In preclinical studies, few problems to overcome are improving stem cells life span in brain after stem cell transplantation, reducing the risk of tumor formation and the integration of transplanted cells into the normal neuronal pathways [4].

Clinical Trials: -

Currently,12 clinical trials are going around the world by using stem cells for the treatment of cerebral palsy. Among in seven have been completed,1is active but not recruiting and 4 of these are recruiting. The mainly used cells are bone marrow delivered stem cells (or) blood delivered mono nuclear cells. Less commonly used are umbilical cord blood containing UC-MSCS and HSCS. All these clinical trials have passed the initial stages of clinical trials. The interventions are correct dosage and safety of stem cell transplantation [4][10].

Inclusion Criteria for Study: -

- 2-12yrs of age at the time of screening for inclusion in the study.
- Non-progressive motor disability due to brain distinction.
- Gross-motor function score II-V
- Gender: -All genders are eligible for study clinical phase [2].

Exclusion Criteria for Study: -

- Medical history of treatment brain injury
- Genetic disorders
- Renal insufficiency
- Hepatic diseases
- Immuno suppression
- HIV+ve
- Infusion related to neurological injury
- Interactive seizure's
- Etiologies of degenerative and metabolic disorders
- Batten disease
- Leukodystrophies
- Neurotransmitter disorders
- Micro and macro cephalic, cortical malfunction
- Acute illness such as fever, vomiting, diarrhea wheezing(or)crackles
- Pulmonary disease requiring ventilator support
- Contraindications to MRI. [2]

Risk of Treatment: -

- Transmission of viral infections
- Causes of encephalopathy
- Risk of allogenic cells and Tumor formation [4][8]

The primary risk of stem cell transplantation is due to allogenic transplants which causes graft Vs host disease in the recipient. Other complications include malignancies, Heparin (or) cytomegalo viruses infection [4]. Woodward et al [22] reviewed 500 patients to receive hemapoitic stem cells transplantation for several diseases. Among them 30pts experienced encephalopathy, organ failure, seizures, medication reaction, Acute disseminated encephalomyelitis, stroke and thrombocytopenic purpura [8].

CONCLUSION

Stem cell transplantation trails held in US and other foreign countries revealed the benefits of stem cells in the treatment of cerebral plasy. All the studies are still ongoing with limited benefits like

- Changes in motor performance
- Changes in white matter tracts
- Repaired the brain damage by releasing growth factor
- Replace the lost and damage neurons

Along with these benefits the individual is leading his life safely with decreased mortality rate. The risk associated with the treatment are managed with the use of some medicament.

REFERENCES:

1. https://www.cerebralpalsy.org/about-cerebral-palsy/definition
2. https://clinicaltrials.gov/ct2/show/record/NCT03078621?term=cerebral+palsy+AND+stem+cells&rank=1&view=recor
3. Nassim H. Abi Chahine, Tarek W. Wehbe, Ramzi A. Hilal, Victoria V. Zoghbi4, Alia E. Melki, Emil B. Bou Habib- Treatment of Cerebral Palsy with Stem Cells: A Report of 17Cases, International Journal of Stem Cells Vol. 9, No. 1, 2016.
4. Stephanie Beldick Michael G.Fehlings -Current State of Stem Cell Treatments for Cerebral Palsy: A Guide for Patients, Families, and Service Providers January,2017.

5. Reddihough, D.S. and K.J. Collins, the epidemiology and causes of cerebral palsy. Aust J Physiother, 2003. 49(1): p. 7-12.
6. Australian Government National Health Medical Research Council (NHMRC), Stem Cell Treatments – A quick guide for medical practitioners,. 2013(Dec 2013, NHMRC Ref #RM01).
7. Australian Government National Health Medical Research Council (NHMRC). Stem Cells, Cloning and Related Issues Online, available: http://www.nhmrc.gov.au/healthethics/human-embryos-and-cloning/stem-cells-cloning-and-related-issues 2013 [last accessed 22 May 2014].
8. https://www.eurostemcell.org/cord-blood-stem-cells-current-uses-and-future-challenges Update On Stem Cell Therapy For Cerebral Palsy- https://www.researchgate.net/publication/49815673
9. Crystal Ruff, Jared Wilcox, Michael Fehlings: Stem cell treatments for cerebral palsy: factsheet for patients and families, February 2011.
10. Carroll JE, Borlongan C. Adult stem cell therapy for acute brain injury in children. CNS & Neurological Disorders – Drug Targets 2008; 7:361–369. [PubMed: 18991664] * A summaries of the benefits of stem cells in acute injury.
11. Jiang Y, Jahagirdar B, Reinhardt R, et al. Pluripotency of mesenchymal stem cells derived from adult marrow. Nature 2002; 418:41–49. [PubMed: 12077603].
12. Jiang T, Vaessen B, Lenvik T, et al. Multipotent progenitor cells can be isolated from postnatal murine bone marrow, muscle, and brain. Exp Hematology 2002; 30:896–904.
13. Yasuhara T, Hara K, Maki M, et al. Intravenous grafts recapitulate the neurorestoration afforded by intracerebrally delivered multipotent adult progenitor cells in neonatal hypoxic-ischemic rats. Journal of Cerebral blood Flow and Metabolism 2008; 28:1804–1810. [PubMed: 18594556] * Demonstrates equivalent benefit of intravenous administration.
14. Reiss P, Zhang C, Saatman K, et al. Transplanted neural stem cells survive, differentiate, and improve neurological motor function after experimental traumatic brain injury. Neurosurgery 2002; 51:1043–1052. [PubMed: 12234415]
15. Zhao LR, Duan WM, Reyes M, et al. Human bone marrow stem cells exhibit neural phenotypes and ameliorate neurological deficits after grafting into the ischemic brain of rats. Exp Neurology 2002; 174:11–20.
16. Kopen GC, Prockop DG, Phinney DG. Marrow stromal cells migrate throughout forebrain and cerebellum, and they differentiate into astrocytes after injection into neonatal mouse brains. Proc Natl Academy Sci 1999; 96:10711–10716.
17. Borlongan CV, Lind DG, Dillon-Carter O, et al. Bone marrow grafts restore cerebral blood flow and blood brain barrier in stroke rats. Brain Res 2004; 1010:108–116. [PubMed: 15126123]
18. Mahmood A, Lu D, Chopp M. Intravenous administration of marrow stromal cells (MSCs) increasers the expression of growth factors in rat brain after traumatic brain injury. J Neurotrauma 2004; 21:33–39. [PubMed: 14987463].
19. Vendrame M, Gemma C, Pennypacker KR, et al. Cord blood rescues stroke-induced changes in splenocyte phenotype and function. Exp Neurology 2006; 199:191–200. 55.
20. Walker PA, Shinil KS, Jimenez F, et al. Intravenous multipotent adult progenitor cell therapy for traumatic brain injury: Preserving the blood brain barrier via an interaction with splenocytes. Experimental Neurology 2010; 225:341–352. [PubMed: 20637752].
21. Rubin J, Wide K, Rermberger M, et al. Acute neurological complications after hematopoietic stem cell transplantation in children. Pediatric Transplantation 2005; 9:62–67. [PubMed: 15667614].
22. Woodward P, Helton K, McDaniel H, et al. Encephalopathy in pediatric patients after allogeneic hematopoietic stem cell transplantation is associated with a poor prognosis. Bone Marrow Transplantation 2004; 33:1151–1157. [PubMed: 15077130]
23. Oskoui, M; Coutinho, F; Dykeman, J; Jetté, N; Pringsheim, T (Jun 2013). "An update on the prevalence of cerebral palsy: a systematic review and meta-analysis". Developmental Medicine & Child Neurology. 55 (6): 509–19.
24. John Yarnell (2013). Epidemiology and Disease Prevention: A Global Approach (02 ed.). Oxford University Press. p. 190. ISBN 9780199660537.
25. Johnson, Ann (2002). "Prevalence and characteristics of children with cerebral palsy in Europe". Developmental Medicine & Child Neurology. 44 (9): 633–40. doi:10.1111/j.1469-8749. 2002.tb00848. x. PMID 12227618.
26. https://www.eurostemcell.org/cerebral-palsy-how-could-stem-cells-help
27. Trabacca, Antonio; Vespino, Teresa; Di Liddo, Antonella; Russo, Luigi (September 2016). "Multidisciplinary rehabilitation for patients with cerebral palsy: improving long-term care". Journal of Multidisciplinary Healthcare. 9: 455–462. doi: 10.2147/JMDH.S88782.PMC 5036581. PMID 27703369
28. O'Shea, TM (2008). "Diagnosis, Treatment, and Prevention of Cerebral Palsy". Clinical Obstet Gynecol. 51 (4): 816–28. doi: 10.1097/GRF.0b013e3181870ba7. PMC 3051278. PMID 18981805.
29. McIntyre, S; Morgan, C; Walker, K; Novak, I (Nov 2011). "Cerebral palsy--don't delay". Developmental Disabilities Research Reviews. 17 (2): 114–29. doi:10.1002/ddrr.1106. PMID 23362031.
30. McGinley, Jennifer L.; Pogrebnoy, Dina; Morgan, Prue (2014). "Mobility in Ambulant Adults with Cerebral Palsy — Challenges for the Future". In Švraka, Emira. Cerebral Palsy - Challenges for the Future. doi:10.5772/58344. ISBN 978-953-51-1234-1.

31. https://en.m.wikipedia.org/wiki/Mesenchymal_stem_cell
32. Takahashi K., Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006; 126:663–676. doi: 10.1016/j.cell.2006.07.024. [PubMed]
33. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4413017/
34. https://www.researchgate.net/publication/318967327_CEREBRAL_PALSY_CAN_CELL_THERAPY_PROVIDE_A_VIABLE_OPTION_IN_THE_TREATMENT_OF_THE_NEUROLOGICAL_DISORDER
35. Satterthwaite AB, Burn TC, Le Beau MM, Tenen DG (Apr 1992). "Structure of the gene encoding CD34, a human hematopoietic stem cell antigen". Genomics. 12 (4): 788–94. doi:10.1016/0888-7543(92)90310-O. PMID 1374051.
36. https://www.sciencedirect.com/topics/immunology-and-microbiology/cd34
37. Nishiyama A, Komitova M, Suzuki R, Zhu X (January 2009). "Polydendrocytes (NG2 cells): multifunctional cells with lineage plasticity". Nature Reviews. Neuroscience. 10 (1): 9–22. doi:10.1038/nrn2495. PMID 19096367.
38. Swiss VA, Nguyen T, Dugas J, Ibrahim A, Barres B, Androulakis IP, Casaccia P (April 2011). Feng Y, ed. "Identification of a gene regulatory network necessary for the initiation of oligodendrocyte differentiation". PLOS One. 6 (4): e18088. Bibcode: 2011PLoSO.618088S. doi: 10.1371/journal.pone.0018088. PMC 3072388. PMID 21490970.